PAWI-2 overcomes tumor stemness and drug resistance via cell cycle arrest in integrin beta3-KRAS-dependent pancreatic cancer stem cells.

Journal: Sci Rep

Publication Year: 2020

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PubMed link: 32514015

Funding Grants: Human Pancreatic Cancer Stem Cells: Developing a Novel Drug for Cancer Eradication

Public Summary:
Today, pancreatic cancer (PC) remains a major health problem in the US. The fact that cancer stem cells (CSCs) become enriched in humans following anti-cancer therapy implicates CSCs as key contributors to tumor dormancy, metastasis, and relapse in PC. A highly validated CSC model (FGβ3 cells) was used to test a novel compound (PAWI-2) to eradicate CSCs. Compared to parental bulk FG cells, PAWI-2 showed greater potency to inhibit cell viability and self-renewal capacity of FGβ3 cells. For FGβ3 cells, dysregulated integrin β3-KRAS signaling drives tumor progression. PAWI-2 inhibited β3-KRAS signaling independent of KRAS. This is clinically relevant. PAWI-2 targeted the downstream TBK1 phosphorylation cascade that was negatively regulated by optineurin phosphorylation via a feedback mechanism. This was confirmed by TBK1 genetic knockdown or co-treatment with TBK1-specific inhibitor (MRT67307). PAWI-2 also overcame erlotinib (an EGFR inhibitor) resistance in FGβ3 cells more potently than bortezomib. In the proposed working model, optineurin acts as a key regulator to link inhibition of KRAS signaling and cell cycle arrest (G2/M). The findings show PAWI-2 is a new approach to reverse tumor stemness that resensitizes CSC tumors to drug inhibition.

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